Liver transplant for CCA and other tumors

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- Cholangiocarcinoma
- Neuroendocrine
- Angiosarcoma
- Hepatic Epithelioid Hemangioendothelioma
- Metastatic colon cancer
Cholangiocarcinoma

- 2nd most common primary hepatic malignancy
  - 10–15% of all hepatobiliary tumors in the USA

- Incidence has been increasing worldwide

- Resection is the treatment of choice in all subtypes of CCA
  - Median OS for R0 in hilar & intrahepatic CCA: 30 & 80 mo. respectively
  - 5 yr. OS is 25%
  - Majority of patients expire due to local tumor recurrence within 2 yrs. of resection

- Risk factors differ based on geographic location
  - In the East, parasitic infections with Opisthorchis viverrini (OV) or Clonorchis is endemic
  - In the West, PSC is the most common known risk factor

5 year OS 5%

Intrahepatic CCA risk factors:
- Cholelithiasis (OR 10.08)
- Cirrhosis (OR 15.32)
- Cholelithiasis (OR 3.36)
- HBV (OR 4.67)
- HCV (OR 4.28)
- Alcohol (OR 3.15)
- Cholelithiasis (OR 1.75)
- Cholecystitis (OR 1.73)
- Smoking (OR 1.25)

Extrahepatic CCA risk factors:
- Cholelithiasis (OR 34.94)
- Cholelithiasis (OR 18.58)
- Cirrhosis (OR 3.82)
- Cholelithiasis (OR 5.92)
- HBV (OR 2.11)
- Alcohol (OR 1.75)
- Cholelithiasis (OR 2.85)
- IBD (OR 2.37)
- T2DM (OR 1.50)
- Smoking (OR 1.09)
CCA & Liver Transplant

MELD Upgrade

- iCCA (intrahepatic) 10-20%
- pCCA (perihilar) 50-60%
- dCCA (distal) 20-30%

Very Early iCCA

BUT

NO

SELECTED

YES

NO

Resection in pCCA

- Resection is SOC, except PSC due to high risk of multifocal CCA

- Limited by:
  - chronic liver disease
  - often infiltrative
  - proximity to critical adjacent vascular structures
  - concern for inadequate liver remnant

- R0 is possible 70-80%

- 5 yr. OS depends on
  - If Negative margins: 27 -45%
  - If Negative LN: 40 - 45%

Anatomical contraindications for resection:
- Encasement of PV: relative, can reconstruct
- Unilateral ductal dilation with contra lateral vascular encasement
- Unilateral atrophy with either contralateral ductal or vascular involvement
OLT for pCCA

- Early experience of OLT for unresectable pCCA with LT alone was poor
  - 5 yr. OS: 23%, recurrence rate: 51%

- Neoadjuvant protocols successful OLT for pCCA

- ITT OS:
  - 1, 3 & 5 yrs. of 82%, 62% & 56%, respectively

- Post-LT OS:
  - 1, 3 & 5 yrs. 91%, 81% & 74%, respectively
  - Superior 5 yr. OS in PSC c/w de novo (80% vs. 64%).
  - Recurrence: 17%

Multicenter Study of LT for pCCA

- 12 US centers; n = 287 (N = 193 from Mayo)
- ITT OS after therapy: 53%
- 5 yr. RFS post LT 65%
- 25% of patients dropped out prior to LT
  - drop-out rate per 3 months averaged 11.5%

- Negative factors:
  - Older age
  - Larger tumor size (> 3 cm)
  - Prior cholecystectomy
  - Prolonged waiting time
  - CA 19-9 > 100 IU

- PSC vs. de novo CCA
  - 5 yr. OS 77% vs.. 56%
  - PSC patients younger, dx at earlier stage & less likely to have pathologic confirmation of CCA
Listing Criteria for pCCA

Unresectable in de novo CCA OR CCA in PSC

1. Diagnostic luminal cytology/biopsy (via endoluminal or percutaneous transhepatic route, not transperitoneal OR
2. Malignant-appearing stricture & at least 1 of the following:
   a. CA19-9 > 100 IU in the absence of cholangitis, or
   b. Aneuploidy by FISH, or
   c. Mass on cross sectional imaging at site of the stricture

○ Cytology
  • Meta-analysis (11 studies; 747 pts.)
    • Sensitivity 43%; specificity 97%

○ Cholangioscopy
  • Meta-analysis (4 studies)
    • Sensitivity 65%, specificity 95%

○ FISH improves brush cytology sensitivity to 89%

○ Newer FISH probe superior diagnostic properties in PSC and Non-PSC
  • gain of 1q21, 7p12, and/or 8q24 and/or loss of 9p21

Extent of Residual Tumor Predicts DFS

<table>
<thead>
<tr>
<th>ERT of N = 152 Explants</th>
<th>5 yr. DFS</th>
</tr>
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<tbody>
<tr>
<td>complete/near-complete response (≤1% ERT)</td>
<td>74%</td>
</tr>
<tr>
<td>marked response (&gt;1 to &lt;10% ERT)</td>
<td>57%</td>
</tr>
<tr>
<td>moderate response (10 to &lt;30% ER)</td>
<td>16%</td>
</tr>
<tr>
<td>minimal response (≥30% ERT)</td>
<td>9%</td>
</tr>
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</table>

○ Pts. with high risk features on explant enrolled in an adjuvant therapy protocol
  • Convert FK to Sirolimus
  • GEM/CIS month 4-10 post LT
  • Imaging month 4 & 12 post LT & then annual
Complications Associated with pCCA Therapy

- Hepatic decompensation
- Acute cholangitis & cholecystitis
- Liver abscess
- GI ulcers
- Delayed gastric emptying
- DVT/PE

- Post LT
  - PV stenosis
    - DDLT vs. LDLT
      - 22.8% vs. 35%
  - HA thrombosis and stenosis
    - LDLT vs. DDLT
      - Thrombosis 8.3% vs. 20.3%, \( P = .041 \)
      - Stenosis 5% vs. 16.7%, \( P = .018 \)

Was cancer ever present?

- Murad et al reported
  - 87 patients (30%) had negative biopsy/brushing
  - 55 patients had residual tumor on explant despite neo adjuvant therapy
  - Remaining 32 patients
    - 17 patients had mass or CA 19-9 > 100 IU w/o obstruction
    - 5% had LT based on clinical suspicion
      - Excluding these patients in analysis resulted in similar results

- 53% of patients with PSC w/o pathologic conformation of CCA prior to chemo/RT had
  - + staging procedure after neoadjuvant therapy
  - Residual tumor on explant
  - Recurrence of CCA post-LT
PSC Associated CCA

- Life time risk: 6.8 -13%
  - 26% in patients with dominant stricture
- Diagnosis of CCA is often within 1-2 yrs. of diagnosis of PSC
- CCA tends to be multifocal (even w/o advanced fibrosis)
  - Neoadjuvant therapy followed by LT

Screening
- CA 19-9 and MRCP

Investigate for CCA:
- Worsening LFTs
- New dominant stricture, bile duct focal thickening/ enhancement on MRCP
- CA 19-9 > 100 IU (w/o cholangitis)
- Bile duct obstruction

Transplantation versus Resection for Hilary Cholangiocarcinoma:
An Argument for Shifting Treatment Paradigms for Resectable Disease

- Retrospective study: 2000-2015; 10 centers compared resection (R0) vs. LT (confirmed H-CCA)

<table>
<thead>
<tr>
<th></th>
<th>Resection (N = 191)</th>
<th>LT (N = 41)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs.)</td>
<td>65</td>
<td>52</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>PSC (%)</td>
<td>2</td>
<td>61</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Chemo &amp;/or RT (%)</td>
<td>57</td>
<td>98</td>
<td>&lt; 0.001</td>
</tr>
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</table>

- Outcomes superior with LT

<table>
<thead>
<tr>
<th></th>
<th>3 yr. OS: LT vs. RS</th>
<th>5 yr. OS: LT vs. RS</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>72% vs. 33%</td>
<td>64% vs. 18%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>RS for tumors &lt;3cm with lymph-node negative disease, and excluding PSC</td>
<td>54% vs. 44%</td>
<td>54% vs. 29%</td>
<td>0.03</td>
</tr>
</tbody>
</table>

Ongoing trial, TRANSPHIL study is looking at OS in resectable CCA after being treated with neoadjuvant therapy followed by LT vs. resection

After adjusting for tumor size, PSC and LN status, LT was associated with improved OS in ITT; P = 0.049
Intrahepatic Cholangiocarcinoma (iCCA)

- Poor outcomes
  - 5-yr. OS < 5%
  - Increase in Incidence worldwide

- Distinction between iCCA and HCC needed
  - Poor prognosis w/ ICCA w/ high recurrence rates
  - No MELD upgrade for iCAA

Intraheaptic Cholangiocacinoma

- Can currently be ONLY be diagnosed via biopsy

<table>
<thead>
<tr>
<th>Size (cm)</th>
<th>Imaging Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 2 cm</td>
<td>Early enhancement that persists in later phases</td>
</tr>
<tr>
<td>&gt; 2 cm</td>
<td>Early peripheral enhancement followed by progressive enhancement of rest of lesion</td>
</tr>
</tbody>
</table>

- Treatment options:
  - Resection with lymphadenectomy
  - Ablation
  - TARE

- Liver transplant around the world has largely been contraindicated

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Resection for iCCA

- 756 pts. with iCCA resected in Japan
  - 419 with complete data set
  - Multivariate analysis of clinicopathologic factors
  - Cutoff of 2 cm used to discriminate OS

5 yr. OS of 15 patients with iCCA ≤ 2 cm w/o LN metastasis or VI = 100%; T1
  - ≤ 2 cm with + VI; 60% OS @ 2 yrs.

- 267 pts. with N0M0 independent prognostic factors:
  - Tumor #
  - presence arterial invasion
  - presence major biliary invasion

OLT for iCCA

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Study design</th>
<th>n</th>
<th>Overall survival (%)</th>
<th>DFS (%)</th>
<th>Neoadjuvant treatment</th>
<th>Adjuvant treatment</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Settiopoulos et al. 2008</td>
<td>2008</td>
<td>Retrospective Multicentre</td>
<td>10</td>
<td>1 year: 70, 90, 50, 33</td>
<td>-</td>
<td>none</td>
<td>none</td>
<td>-</td>
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<tr>
<td>Vallin et al. 2013</td>
<td>2013</td>
<td>Multicentre</td>
<td>10</td>
<td>2 year: 80, 60, 24</td>
<td>-</td>
<td>none</td>
<td>none</td>
<td>-</td>
</tr>
<tr>
<td>Sapisochin et al. 2014</td>
<td>2014</td>
<td>Retrospective Multicentre</td>
<td>27</td>
<td>3 year: 78, 66, 51, 35</td>
<td>-</td>
<td>none</td>
<td>none</td>
<td>-</td>
</tr>
<tr>
<td>Faccio et al. 2015</td>
<td>2015</td>
<td>Multicentre</td>
<td>71</td>
<td>5 year: 71, 57, 44</td>
<td>-</td>
<td>none</td>
<td>none</td>
<td>-</td>
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<tr>
<td>Völler et al. 2016</td>
<td>2016</td>
<td>Retrospective Multicentre</td>
<td>440</td>
<td>1 year: 79, 58, 47</td>
<td>-</td>
<td>none</td>
<td>none</td>
<td>-</td>
</tr>
<tr>
<td>Sapisochin et al. 2016</td>
<td>2016</td>
<td>Single ±2 cm Multicentre</td>
<td>10</td>
<td>1 year: 93, 84, 65, 62</td>
<td>-</td>
<td>none</td>
<td>none</td>
<td>-</td>
</tr>
<tr>
<td>Mázey et al. 1999</td>
<td>1999</td>
<td>Retrospective Multicentre</td>
<td>33</td>
<td>1 year: 79, 90, 45, 39</td>
<td>-</td>
<td>none</td>
<td>none</td>
<td>-</td>
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<tr>
<td>O'Connor et al. 2001</td>
<td>2001</td>
<td>Multicentre</td>
<td>84</td>
<td>5 year: 62, 39, 35</td>
<td>-</td>
<td>none</td>
<td>none</td>
<td>6 patients with HCC</td>
</tr>
<tr>
<td>Raber et al. 2004</td>
<td>2004</td>
<td>Retrospective Multicentre</td>
<td>32</td>
<td>1 year: 77, 65, 42</td>
<td>-</td>
<td>none</td>
<td>none</td>
<td>2-year DFS 33%</td>
</tr>
<tr>
<td>Ghall et al. 2005</td>
<td>2005</td>
<td>Retrospective Multicentre</td>
<td>30</td>
<td>1 year: 72, 48, 23</td>
<td>-</td>
<td>none</td>
<td>none</td>
<td>1 patient with HCC</td>
</tr>
<tr>
<td>Hong et al. 2007</td>
<td>2007</td>
<td>Retrospective Multicentre</td>
<td>32</td>
<td>1 year: 72, 38, 33</td>
<td>-</td>
<td>none</td>
<td>none</td>
<td>9 and IT no LT</td>
</tr>
<tr>
<td>Lansford et al. 2018</td>
<td>2018</td>
<td>Prospective single-arm</td>
<td>12</td>
<td>1 year: 83.3, 83.3</td>
<td>-</td>
<td>none</td>
<td>none</td>
<td>1 patient with HCC</td>
</tr>
</tbody>
</table>

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Sakamoto Y et al. Cancer 2010;122(1):61-70
Liver Transplant for Intrahepatic CCA

- Retrospective study 01/00 – 12/13
- 17 international transplant centers
- All patients had OLT for presumed HCC or decompensated cirrhosis w/o evidence of a lesion
- Groups:
  - Very early iCCA: single lesion ≤ 2 cm
  - Advanced iCCA: single lesion > 2 cm or > 1 lesion
  - Very early iCCA + HCC (different nodules)
  - Advanced iCCA + HCC (different nodules)

Multivariate analysis for risk of recurrence:
- poorly differentiated tumor (0% in very early iCCA)
- + microvascular invasion (13% in very early iCCA)

Intermediate stage 2.1 – 3.0 cm w/o poorly differentiated tumor n=6
1, 3 & 5 yr. OS: 82%, 61%, 61%

Advanced iCCA N=27
1, 3 & 5 yr. OS: 55%, 47%, 42%

National Cancer Data Base
- Identified iCCA ≤ 2 cm & OLT 2004 – 2012

N = 22

<table>
<thead>
<tr>
<th></th>
<th>All</th>
<th>LN staged at LT &amp; negative (n = 9)</th>
<th>LN not staged at LT (n = 13)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 yr. OS (%)</td>
<td>91</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>3 yr. OS (%)</td>
<td>70</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>5 yr. OS (%)</td>
<td>56</td>
<td>67</td>
<td>47</td>
</tr>
</tbody>
</table>

- No impact of adjuvant chemotherapy or radiotherapy on outcomes
Liver Transplant for Intrahepatic CCA

- Retrospective, single center study of patients transplanted for HCC within MC but diagnosed with iCCA or cHCC-CCA on explant

<table>
<thead>
<tr>
<th></th>
<th>Early iCCA (n =12)</th>
<th>HCC MC + (N = 319)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 yr. OS</td>
<td>63.6%</td>
<td>90.0 %</td>
</tr>
<tr>
<td>5 yr. OS</td>
<td>63.6%</td>
<td>70.3%</td>
</tr>
<tr>
<td>Recurrence</td>
<td>33.3%</td>
<td>11%</td>
</tr>
</tbody>
</table>

- iCCA patients were more likely to be understaged and have higher tumor grade and + VI compared to HCC

Prognostic markers for iCCA

- Not detectable in 7% of population due to lack of Lewis Ag
- Elevated with benign biliary disease or cholangitis
- Level significantly associated with cirrhosis & LN metastasis and OS (> 37 U/ml)
Liver Transplant for Neuroendocrine Tumors

- Approximately ½ of NET patients develop liver metastasis & OFTEN is only site of metastatic Dz
  - 5-yr. OS 19 -38%
  - 80% of time is unresectable

- Largest review of > 1100 patients from registries
  - 5 yr. OS 63%
  - Recurrence ranged from 30 - 60%
  - Predictors of decreased OS:
    - > 50% Liver involvement, high Ki67 index & pancreatic NET (vs. GI)

- LT: intent of cure rather than palliation
  - Milan criteria for LT for NET
    - 5- & 10- yr. OS 97% and 89%, respectively (n=42) vs.
    - 51% & 22%, respectively, similar tumor burden treated with a non-transplant strategy (N=46)

- Confirmed histology of G1 or G2 tumor
- Primary tumor drained by the portal system
- Hepatic involvement of <50%
- Complete resection of primary tumor and all extrahepatic disease with stable disease or good response to therapies for at least 6 mo.
- Age<60 years (relative criteria).

Liver Transplantation for Colorectal and Neuroendocrine Liver Metastases and Hepatoblastoma. Working Group Report From the ILTS Transplant Oncology Consensus Conference

1. LT should be considered as a potentially curable treatment option for selected patients with unresectable metastatic NET of midgut/hindgut origin confined to the liver (moderate level of evidence and strong recommendation).
2. Selection criteria should consider $^{68}$Ga-DOTATATE, Ki67, histology, site of origin, and a certain time interval of stable disease or good response to therapies (moderate level of evidence and strong recommendation).
3. LT for selected patients with metastatic NET confined to the liver as part of multimodality therapy should achieve comparable outcomes as LT for other diagnoses (moderate level of evidence and strong recommendation).
4. Everolimus has achieved improvement in progression-free survival in NET and should be considered as part of immunosuppression after LT for NETLM (low level of evidence and strong recommendation).
5. Late recurrences beyond 5 years after LT are not uncommon, necessitating long-term follow-up with annual imaging (moderate level of evidence and strong recommendation).
Hepatic Angiosarcoma

- Rare tumor; 3rd most common liver tumor
- Single mass with satellite lesions of infiltrative mass with atypical proliferation of endothelial cells in sinusoids
- High mortality: 2° rupture / liver failure
  - 2 year OS 3%
- Risk factors: vinyl chloride, arsenic, cyclophosphamide, anabolic steroids, OCP
- Therapy: resection + chemotherapy
  - OLT contraindicated; poor outcomes

Hepatic Epithelioid Hemangioendothelioma

- Rare tumor: vascular origin; < 1 per million people
- Non specific sx: RUQ pain, wt loss, BCS, abnormal liver function
- Generally low to intermediate grade
  - More favorable prognosis than other hepatic malignancies
- Commonly middle age female, median age 41
- Dx made by biopsy: Stains: + for 1 of the following endothelial markers:
  - Factor VIII-related Ag, CD34, CD31
  - Negative for epithelial markers: cytokeratin and CEA:
    - MUST distinguish from adenocarcinoma or sarcoma
- Course: prolonged survival to rapidly progressive course
- Treatment:
  - Resection
  - OLT: >10 nodules or >4 involved hepatic segments
  - Anti VEGF therapy
Hepatic Epithelioid Hemangioendothelioma

Peripheral confluent mass with capsular retraction is the hallmark feature

Peripheral coalescing masses with capsular retraction

Multiple peripheral masses w/ capsular retraction & more confluent lesions centrally w/calcification.

LT for HEHE

- European Liver Transplant Registry
- 149 patients transplanted for HEHE; Median post-LT follow-up was 7.6 years
- Predictors of recurrence:
  - macrovascular invasion (hazard ratio [HR], 4.8; P < 0.001)
  - pre-LT waiting time of 120 days or less (HR, 2.6; P = 0.01)
  - hilar lymph node invasion (HR = 2.2; P = 0.03)

BUT

- pre-LT extrahepatic disease was NOT a significant predictor of recurrence
Rare in cirrhosis
- Alterations in portal flow
- 1st neoplasms can spread to a cirrhotic liver, particularly colorectal adenocarcinoma

> 50% of CRC develop metastasis to the liver

Study at the University of Oslo in Norway of 21 selected patients with unresectable liver metastases showed 5 year OS of 60%
- 4 factors were associated with significantly worse OS
  - Tumor diameter > 5.5 cm
  - CEA > 80 μg/L
  - Interval from resection of primary to LT < 2 yrs.
  - Progression of mets while on chemotherapy

Oslo score: using these 4 factors (0-4)
- 3 groups
  - 0-1, 2-3 & 3-4

1. LT can be a viable option in highly selected patients with unresectable CRLM with only liver involvement (moderate level of evidence and moderate recommendation).
2. LT for CRLM with low Oslo score ≤2 (maximum tumor diameter ≤5.5 cm, pretransplant carcinoembryonic antigen ≤80 μg/L, response to chemotherapy, time interval: diagnosis to LT ≥2 y) may improve the 5-year overall survival rates over those achieved with the current standard of care (moderate level of evidence and moderate recommendation).
3. Minimization of immunosuppression is recommended (low level of evidence and moderate recommendation).
4. Aggressive treatment of all posttransplant resectable recurrences is recommended (low level of evidence and moderate recommendation).
5. There is a need for an international registry to coordinate data collection and design further studies on LT for CRLM (moderate level of evidence and moderate recommendation).
Summary

- LT for pCCA can offer long term OS in selected patients
  - 5 yr. OS of 65%
- PSC + early CCA, LT is the treatment of choice
- LT in De Novo CCA requires the tumor to be unresectable to obtain a MELD exception
- iCCA has been considered a contraindication for LT, however early iCCA, single lesion < 2 cm shows promising results associated with LT
- UNOS has adopted the Milan criteria for NET for LT
- HEHE needs to be distinguished from angiosarcoma which is an absolute contraindication for LT
- MCRC is being explored as an indication for LT in selected patients.

MOC Question

- A 33 y/o male presents with itching and 20 lb. weight loss over 3 months. He is diagnosed with PSC based on MRCP. Scan also shows a dominant stricture in the common hepatic duct with a mass measuring 2.1 cm. Spleen is normal size, no ascites. An ERCP with brushings showed atypical cells, FISH showed polysomy. A stent was placed. He had pancreatitis after ERCP requiring admission

- Labs:
  - Bilirubin 4.5
  - Platelets 200,000
  - INR 1.2
  - Albumin 3.3
  - CA 19-9 185
MOC Question
As the treating hepatologist you would recommend the following
1. Resection since he does not appear to have advanced liver disease.
2. Refer for immediate liver transplantation since he has some degree of liver dysfunction
3. Plan for EUS with biopsy to confirm diagnosis of CCA and avoid risk of recurrent pancreatitis.
4. Plan for resection and if recurs, then plan for liver transplant.
5. Refer to oncology for chemoradiation and refer for LT evaluation.

MOC Question
1. LT rather than resection is the treatment of choice in a patient with PSC with CCA as it is often multifocal
2. LT without neoadjuvant therapy have shown poor outcomes.
3. Transperitoneal biopsy is contraindicated if LT is planned due to increase risk of metastatic disease post LT. The patient meets diagnostic criteria for CCA without need for tissue
4. Prior resection or attempted resection is an exclusion for LT
5. Neoadjuvant therapy prior to LT has been shown to improve OS post LT.
Which of the following patients is the most reasonable for consideration for LT evaluation

1. 69 y/o male with pancreatic NET metastatic to the liver, primary tumor has not been removed
2. 51 y/o male with cirrhosis with portal HTN with biopsy proven intrahepatic CCA measuring 1.7 cm
3. 35 y/o female with hilar CCA with liver lesions biopsy proven to be CCA
4. 34 y/o female with no known liver disease with bilobar liver lesions that are concerning for hepatic epithelioid hemangioendothelioma.
1. Age > 60 in NET is a relative contraindication, however the primary tumor remaining in place is an exclusion for LT
2. While there is currently no MELD upgrade for very early iCCA, mounting evidence is suggesting that outcomes in such patients may be acceptable
3. Hilar CCA with intrahepatic spread is an exclusion for LT
4. HEHE needs to be diagnosed via biopsy to rule out angiosarcoma which is an absolute contraindication for LT.

References